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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/928,262	08/10/2001	Menzo Jans E. Havenga	4509.1US	6584

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	13

DATE MAILED: 07/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/928,262	Applicant(s) HAVENGA ET AL.	
	Examiner Brian Whiteman	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-8,10,11,24,25,27 and 28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-8,10,11,24,25,27,28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Final Rejection

Claims 1, 5-8, 10, 11, 24, 25, 27, and 28 are pending.

Applicants' traversal, the amendment to the specification, the amendment to claims 1, 5, 6, 7, 8, 10, 11, 24, 25, 27, and 28, the cancellation of claims 2-4 and 9, the amended sequence listing and the new oath/declaration in paper no. 11 filed on 6/2/03 is acknowledged and considered.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in EPO on 8/10/00. It is noted, that applicant has filed a certified copy of the 002022835.5 application as required by 35 U.S.C. 119(b).

Claim Objections

Applicant's arguments, see paper no. 11, filed on 6/2/03, with respect to objection have been fully considered and are persuasive. The objection of claims 10 and 24 has been withdrawn because of the amendment to the claims. See pages 10 of paper no. 11.

Claim Rejections - 35 USC § 112

Applicant's arguments, see paper no. 11, filed on 6/2/03, with respect to 112 first paragraph written description rejection have been fully considered and are persuasive. The

rejection of claims 1-3, 6-8, 10-11, 24, 25, and 27-28 has been withdrawn because of the amendment to the claims and cancellation of claims 2 and 3. See pages 10-11 of paper no. 11.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5-8, 10, 11, 24, 25, 27, and 28 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of delivering of delivering a nucleic acid of interest to a primary human chondrocyte *in vitro* comprising infecting the isolated human chondrocyte with a recombinant adenovirus based on adenovirus serotype 5 having a tropism for primary human chondrocyte, wherein said tropism is provided by at least a tropism determining a part of an adenoviral fiber protein of an adenoviral fiber protein of a B-type adenovirus, does not reasonably provide enablement for a method for delivering a nucleic acid of interest to a primary chondrocyte comprising providing a recombinant adenovirus having a tropism for primary human chondrocytes and for a method of inhibiting cartilage disease progression or repairing cartilage in a human using the claimed recombinant adenovirus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention is directed to making a recombinant adenovirus having a tropism for primary human chondrocytes and using the adenovirus for delivering a nucleic acid to a

primary human chondrocytes. More specifically, the claimed invention is directed to using the adenovirus a method of inhibiting cartilage disease progression or repairing cartilage in a human. The invention lies in the field of gene therapy for treating a cartilage disorder in a human.

Furthermore, and with respect to claims directed to any adenoviral vector useful for gene therapy and directed to any treatment of a human; the state of the art exemplified by Anderson et al., *Nature*, Vol. 392, pp. 25-30, April 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method.

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

In addition, gene transduction to chondrocytes has not been well studied (Arai et al. J Rheumatol, Vol. 24, pp. 1787-95, 1997). Many proteins have been reported to protect articular cartilage and are believed to have use as anti-arthritic proteins. However, conventional delivery systems such as oral, intravenous, intramuscular, or intraarticular administration have problems in delivering a drug to a specific joint and maintaining long term therapeutic effect (Arai, page 1787). Arai further states that, "if we can transduce chondroprotective genes into chondrocytes of cartilage, this could be efficient therapy for joint disorders (pages 1787 and 1792)." The art of record further teaches that in vivo methods do not deliver enough genes to chondrocytes in cartilage (Ikeda et al., The Journal of Rheumatology, Vol. 27, pp. 990-6, 2000 and Nixon et al. Clinical Orthopaedics and Related Research, Vol. 379S, pp. S201-213, 2000).

Thus, the state of the art for gene therapy for treating a cartilage disorder is considered unpredictable.

The specification provides examples to illustrate the present invention: Example 1 is the generation of adenovirus serotype 5 genomic 15 plasmid clones. Example 2 is the generation of

adenovirus serotype 5 based viruses with chimer fiber proteins. Example 3 is the production, purification and titration of fiber chimeric adenoviruses. Example 4 is testing for the expression on primary chondrocytes for membrane molecules known to be involved n Ad5 infection. Examples 5-7 are adenovirus transduction of human primary human chondrocytes *in vitro*, wherein the adenovirus comprises a marker gene.

In addition, the specification only provides sufficient guidance for a method of delivering of delivering a nucleic acid of interest to a primary human chondrocyte *in vitro*. The specification does not provide a working example for the claimed method of treating a cartilage disorder using the claimed recombinant adenovirus. The specification does not display how marker gene expression reasonably extrapolates to repairing cartilage in a human or inhibiting cartilage disease progression in a human. The art of record teaches the unpredictability of *in vivo* delivery of a nucleic of interest to a specific cell (chondrocytes) in a human (see Anderson, Verma, Ikeda). The art of record further teaches that *in vivo* methods do not deliver enough genes to chondrocytes in cartilage to generate a therapeutic response for treating a cartilage disorder in a human (see Ikeda). Therefore, the as-filed specification does not provide sufficient description or factual evidence for one skilled in the art to use the claimed invention.

As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed recombinant adenovirus generates a therapeutic effect, how is it apparent as to how one skilled in the art, without any undue experimentation, practices any nucleic acid therapy method as contemplated by the claims, particularly given the unpredictability of nucleic acid therapy as a whole and/or the doubts expressed in the art of record.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or factual evidence to reasonably enable for a method of delivering of delivering a nucleic acid of interest to a primary human chondrocyte *in vitro* comprising infecting the isolated human chondrocyte with a recombinant adenovirus based on adenovirus serotype 5 having a tropism for primary human chondrocyte, wherein said tropism is provided by at least a tropism determining a part of an adenoviral fiber protein of an adenoviral fiber protein of a B-type adenovirus. Given that gene therapy wherein any adenoviral vector is employed to treat a disease or a medical condition in any human was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any gene delivery vector cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicants' disclosure and the unpredictability of gene therapy.

Applicant's arguments filed 6/2/03 have been fully considered but they are not persuasive. The specification does not teach one skilled in the art how to use the claimed recombinant chimeric adenovirus comprising a nucleotide sequence encoding luciferase (lacZ) operatively linked to a promoter in a method of delivering the nucleotide sequence to a human. In view of the specification it is not apparent to one skilled in the art the use for delivering a lacZ gene to in vivo primary human chondrocytes. It is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement, e.g. Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997).

The court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:
It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.

In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

In view of the art of record, the breadth of the claims, and the lack of guidance provided by the specification, it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from delivering a lacZ gene to primary human chondrocytes *in vitro* to delivering a lacZ gene to primary human chondrocytes *in vivo*. Thus, the specification does not enable one skilled in the art how to use a genus of recombinant adenovirus having a tropism for primary human chondrocytes in the claimed *in vivo* methods.

With respect to the argument citing MPEP 2164.01 and stating that, "it would not take one skilled in the art an undue amount of experimentation to replace the marker gene with a nucleic acid sequence encoding the an amino acid sequence that inhibits cartilage disease progression or that counteracts the loss of cartilage, such as bone morphogeneisis protein (BMP)." The rejection is not found persuasive because the rejection is not based on making the claimed chimeric adenovirus. The rejection is based on using the adenovirus in the claimed methods. In view of the In Re Wands Factors, the specification does not provide sufficient guidance to commensurate with the full scope of the claimed invention. The specification does not teach how to use the chimeric adenovirus in any therapeutic method set forth in the claimed methods. The art of record teaches the unpredictability of gene therapy for treating a cartilage

disease. The art of record further teaches that *in vivo* methods do not deliver enough genes to chondrocytes in cartilage to generate a therapeutic response for treating a cartilage disorder in a human (see Ikeda). Therefore, the as-filed specification does not provide sufficient description or factual evidence for one skilled in the art to make and use the claimed invention.

The court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.

In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

Thus, the 112 first paragraph enablement rejection remains.

Claim Rejections - 35 USC § 102

Applicant's arguments, see paper no. 11, filed on 6/2/03, with respect to 102(b) rejection have been fully considered and are persuasive. The rejection of claims 1-8 has been withdrawn because of the amendment to the claims and cancellation of claims 2 and 3. See page 16 of paper no. 11.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b)

only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 1, 5, 6, 7, and 8 remain rejected under 35 U.S.C. 102(e) as anticipated by Wickham et al. (US Patent 6,455,314, EFD 9/11/98) or, in the alternative, under 35 U.S.C. 103(a) as obvious over Doherty et al. (Osteoarthritis and Cartilage, Vol. 6, pp. 153-160, 1998). Wickham teaches a method of infecting a chondrocytes comprising administering a recombinant chimeric adenoviral virion incorporating a recombinant fiber protein with appropriate cell-specific ligand (column 4, line 45 - column 10, line 1-45). Wickham further teaches that through fiber incorporation the protein would exhibit reduced affinity for a native substrate than does a wild-type adenoviral fiber trimer and integration of an appropriate cell-specific ligand, the virion can be employed to target any desired cell type including chondrocytes (abstract and column 9, line 20-column 10, line 67). The recombinant fiber protein can be from B-serotype adenovirus 35 (column 4, lines 28-41). In addition, Wickham teaches *in vivo* recombinant adenoviral vector gene delivery, wherein the adenoviral vector comprises a modified fiber protein. The recombinant adenoviral vector would transfect many cells, including chondrocytes. Wickham does not specifically teach infecting human chondrocytes, however, Doherty teaches that human chondrocytes were used in adenovirus vector-gene transduction studies. This teaching shows that one of skill in the art would interpret the chondrocytes of Wickham to be human.

Applicant's arguments filed 6/2/03 have been fully considered but they are not persuasive because Wickham teaches making and using a chimeric adenovirus virion incorporating a

recombinant fiber protein with appropriate cell-specific ligand, wherein the recombinant fiber protein is B-serotype adenovirus 35 (column 4, lines 28-41).

In addition, the argument on page 15 of applicant's response (Wickham does not have an enabling disclosure of providing a recombinant chimeric adenovirus having a tropism for primary human chondrocytes) is not found persuasive because MPEP 2121 states:

> When the reference relied on expressly anticipates or makes obvious all of the elements of the claimed invention, the reference is presumed to be operable. Once such a reference is found, the burden is on applicant to provide facts rebutting the presumption of operability. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). See also MPEP § 716.07.

This is the case here since Wickham teaches how to make and use the recombinant chimeric adenovirus set forth in the claimed embodiment.

Furthermore, the argument on page 15 of applicant's response is not found persuasive because MPEP § 716.01(c) states:

> The arguments of counsel cannot take the place of evidence in the record. In re Schulze,346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant.

Claim Rejections - 35 USC § 103

Applicant's arguments, see paper no. 11, filed on 6/2/03, with respect to 103(a) rejection have been fully considered and are persuasive. The rejection of claims 1, 11, and 24, and 25 has been withdrawn because of the amendment to the claims. See pages 16-18 of paper no. 11.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER